

# THERAPEUTICS

## Cholesterol trials and mortality

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**Received** 16 December 2015; **revised** 17 March 2016; **accepted** 17 March 2016

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**Keywords** cholesterol, statin, fibrates, epidemiology, regulation, mortality, composite endpoints

An overview of clinical trials can reveal a class effect on mortality that is not apparent from individual trials. Most large trials of lipid pharmacotherapy are not powered to detect differences in mortality and instead assess efficacy with composite cardiovascular endpoints. We illustrate the importance of all-cause mortality data by comparing survival in three different sets of the larger controlled lipid trials that underpin meta-analyses. These trials are for fibrates and statins. Fibrate treatment in five of the six main trials was associated with a decrease in survival, one fibrate trial showed a non-significant reduction in mortality that can be explained by a different target population. In secondary prevention, statin treatment increased survival in all five of the main trials, absolute mean increase ranged from 0.43% to 3.33%, the median change was 1.75%, which occurred in the largest trial. In primary prevention, statin treatment increased survival in six of the seven main trials, absolute mean change in survival ranged from –0.09% to 0.89%, median 0.49%. Composite safety endpoints are rare in these trials. The failure to address composite safety endpoints in most lipid trials precludes a balanced summary of risk–benefit when a composite has been used for efficacy. Class effects on survival provide informative summaries of the risk–benefit of lipid pharmacotherapy. We consider that the presentation of key mortality/survival data adds to existing meta-analyses to aid personal treatment decisions.

### Background

Cardiovascular disease is the main cause of death in Western populations [1]. The causes of atheroma are multifactorial. The major risk factors of smoking, high blood pressure, diabetes mellitus, diet and psychosocial factors are well described [2]. From The Seven Countries Study [3] onwards, epidemiology identified cholesterol as a risk factor and total mortality rises steeply with increasing serum cholesterol [4].

The lipid hypothesis stimulated the development of drugs to lower cholesterol and the funding of clinical trials to investigate potential reductions in morbidity and mortality of patients with (secondary prevention) and without (primary prevention) cardiovascular disease. Experience with early drugs, such as cholestyramine, niacin, hormones or fibrates, was disappointing; lowering cholesterol as a biomarker did not automatically translate into patient benefit. The subsequent clinical and commercial success of statins in secondary

prevention of cardiovascular disease led many experts to presume that any decrease in cholesterol leads to a linear reduction in cardiovascular events [5], even though the epidemiology shows a nonlinear relationship between these two variables [4]. The average extension of life expectancy with statins is small, median postponement of death has been calculated as three days for primary and four days for secondary prevention [6]. This is only one way of analysing the data, as benefit will not be evenly spread.

Quantifying outcomes for a balanced assessment of risk–benefit is complex. The adverse event profiles of lipid drugs are difficult to detect and summarize as one endpoint, whereas efficacy in trials is often defined as a predefined composite endpoint. Composite clinical endpoints are useful for testing hypotheses, but when used without corresponding composite safety endpoints they can distort the risk–benefit analysis. Adverse events are rarely pooled, either as composite safety endpoints, or in meta-analyses.

Survival and mortality data have the advantage of generating a scale with a single endpoint, one death caused by treatment has equal weight to one death prevented by treatment. This allows a risk–benefit assessment that can be readily explained to the patient as to whether or not treatment will extend life expectancy. Trial analysis depends on pre-specified primary endpoints, though in regulation mortality has priority in that if more subjects die on treatment then this affects the risk–balance assessment.

We have tabulated mortality data from the major lipid trials to summarize the net effect on all-cause mortality and survival. Trials were chosen that recruited over 1000 patients and included a placebo, or no treatment, arm with intended follow-up of two years or longer. Fibrates were chosen as an example, as the trial data for secondary and primary prevention illustrate the importance of reviewing such drugs as a class. Statin trial data are more extensive, allowing the examination of the different effects on survival of primary and secondary prevention. Trials of more complex populations, such as renal failure or heart failure, have been excluded for simplicity.

Though the effect of treatment on survival has been addressed by meta-analyses, an additional presentation of the key survival data provides information for more contentious areas such as the risk–benefit of fibrates, or primary prevention with statins.

## Why mortality matters in cholesterol trials

Disease-related mortality determines the acceptability of the severity and frequency of treatment-related adverse events. Even a trend in the mortality rate allows the calculation of a 95% confidence interval (CI) of potential risk or benefit, which has been used by regulators to define the likely absence of harm [7].

In most populations death is usually caused by cardiovascular disease or cancer. For cancer, treatment effects can be summarized as the expected mean increase in life expectancy, or the number of patients alive at fixed time points, such as survival at one or two years after treatment. For oncology trials the cause of death, cancer related or not, is not thought relevant. Survival data are fundamental to cardiovascular epidemiology, for example, the loss of 11–12 years of life expectancy for the average smoker, where much of the higher mortality is attributable to myocardial infarction (MI). The gain in life expectancy from stopping smoking is also well known [8, 9].

Mortality data from clinical trials have advantages. They are relatively cheap and easy to collect. Unlike other adverse events, they do not need to be graded for severity. There is no doubt about the diagnosis and there is no need for adjudication committees to resolve borderline cases. Risk–benefit analysis normally involves an imperfect weighing of different scales with complex methods, such as balancing a single composite efficacy endpoint against a myriad of minor signals from adverse events that cannot be summarized readily. Only occasionally does a single scale of a continuous parameter dominate the risk–benefit balance calculation,

such as the incidence of MI with diabetes therapy [7]. Mortality is another example of a symmetrical endpoint in risk–benefit analysis that represents a fair assessment.

Mortality data, such as collected in the four International Studies of Infarct Survival (ISIS-1 to ISIS-4 randomized over 140 000 patients), made a major contribution to cardiovascular prescribing, yet cost a fraction of more complex trials that are not powered for mortality. Mortality differences have been useful in single lipid trials, such as the increase in mortality with torcetrapib, hazard ratio (HR) 1.58; 95% CI, 1.14–2.19;  $P = 0.006$  [10]. It has been proposed that a new preventive therapy for cardiovascular disease should be used sparingly, if at all, until clinical trials establish equivalence to, or even superiority over, existing treatments in terms of mortality from all causes [11].

Though cardiovascular disease is a common cause of death, mortality data are rarely prominent in key lipid trials. The usual explanation is that trials are not powered to detect mortality/survival differences. A recent example is the IMPROVED Reduction of Outcomes: Vytorin Efficacy (IMPROVE-IT) trial [12]. The authors state that a lack of an effect of ezetimibe on all-cause mortality was no surprise, as the size of the trial was not established to detect such an effect [13]. Insufficient power to detect a difference is not the same as a true lack of difference. Editorial enthusiasm for ezetimibe was not supported by mortality benefit [14]. IMPROVE-IT randomized more than four times the population and recorded approximately double the death rate when compared to the Scandinavian Simvastatin Survival Study (4S). If 4S was powered for mortality, then a trial that is roughly eight times as powerful has validity. The 1231/9077 deaths in the control group (13.6%) shows no important difference from the 1215/9067 deaths in the ezetimibe group (13.4%).

Before IMPROVE-IT reported, there was evidence supporting no effect of ezetimibe on mortality from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial, all-cause mortality HR slightly higher with ezetimibe 1.29; 95% CI, 0.82–2.03 [15] and the Study of Heart and Renal Protection (SHARP) trial, all-cause mortality HR 1.01; 95% CI, 0.94–1.11 [16]. A meta-analysis of 27 trials also showed no mortality benefit [17].

Given the benefit of ezetimibe on a cardiovascular composite endpoint, it might affect the pattern of the cause of death by an unknown mechanism. Ezetimibe approximately doubles the synthesis of endogenous cholesterol by the liver [18–20] which might counteract the benefit of statins, but this is conjecture.

It is often difficult to identify whether the cause of death is drug related. A drug may have no net effect on survival, though it affects the pattern of the cause of death within a population. Such a drug can decrease cardiovascular deaths and increase non-cardiovascular deaths to an equal extent, without these effects reaching statistical significance. If cardiovascular deaths are combined with more frequent events, such as non-fatal MI and stroke, unstable angina and coronary revascularisation, to form a single composite endpoint, then statistical significance may be reached. This composite efficacy endpoint confirms the primary pharmacology of the drug, but does little to inform the patient, as the efficacy composite endpoint has no safety composite to act as a counterweight in the assessment of risk–benefit. All patients are

interested in survival, but whether death is cardiovascular, or not, is less relevant to the patient or their relatives.

Non-cardiovascular mortality may not reach statistical significance as a single endpoint, but if combined with other adverse events might achieve significance as a safety composite endpoint. The use of composite endpoints for safety is rare, in contrast to efficacy composites. It is difficult to identify prospectively components of a safety composite when adverse events arise from a range of secondary pharmacology that is often unpredictable.

## Fibrate trials

The mortality data from the main fibrate trials are shown in Table 1 [21–26]. The trials are presented in order of the number of patients recruited. Different primary and secondary populations were studied, with variable inclusion criteria such as males, high cholesterol, diabetes, arterial disease or high triglycerides and low high density lipoprotein (HDL).

Fibrate treatment was associated with an increase in all-cause mortality, the exception being the use of gemfibrozil in the Veterans Affairs HDL Intervention Trial (VA-HIT) [25]. This trial recruited patients with high triglycerides and low HDL concentrations. This is a population which might possibly benefit from fibrates, though the evidence for high triglycerides as a cardiovascular risk factor is debated and total HDL represents a collection of lipid sub-fractions that may vary in their importance for possible cardiovascular protection. However, the potential benefit on survival in this VA-HIT population did not reach significance. A fibrate trial meta-analysis confirmed a 13% reduction in coronary events, but no reduction in cardiovascular mortality, despite the 10–15% lowering of low density lipoprotein (LDL) [27].

A study of French farmers exposed to an ICI crop spray in the 1950s revealed considerable toxicity, including low plasma cholesterol. This changed the development of an agricultural chemical into a drug, clofibrate for hyperlipidaemia,

introduced into clinical practice in 1962 and approved in the USA in 1967. By 1971 benefit in early trials, including favourable mortality data [28, 29], cast doubt on the need to conduct any further clofibrate/placebo controlled trials [30]. Yet the World Health Organisation (WHO) Clofibrate trial, started in 1964, was continued. As is so often the case with a series of clinical trials, as more results from bigger trials became available, the early promise of benefit started to wane [31].

An intermediate-sized clofibrate trial, of almost 4000 men followed for six years, showed no mortality benefit [32].

The largest fibrate trial in terms of recruitment was the WHO Clofibrate trial. The 1978 result is presented, when the blind was broken, though later a 1984 analysis, of some 200 000 patient years, suggested a mean 47% increase in mortality,  $P < 0.01$ , whilst on treatment reduced to a non-significant increase in mortality of 5% when treatment stopped [33]. We are confident about the harm caused by clofibrate, as it is the largest of the major fibrate trials, a trial without a commercial sponsor, where survival status was determined for over 99% of participants. The clofibrate trial supports a hypothesis that fibrates as a class have a negative risk benefit until proven otherwise. None of the subsequent fibrate trials disprove this hypothesis; the results for other fibrates are indistinguishable from the clofibrate trials before the WHO trial reported. If the WHO trial had not been conducted, clofibrate would still be on the market.

A wider approach that does not rely solely on randomized trial results has been described by Professor Sir Michael Rawlins in his Harveian Oration [34]. The Bayesian method is limited by the subjective nature of statistical evaluations of priors. Despite this, the statistical priors for Table 1 are powerful. Chemistry and pharmacology determine class effects. The four fibrates in Table 1 show similar medicinal chemistry. Clofibrate, bezafibrate and fenofibrate share a chlorinated phenoxy methylpropionate structure. They are similar to 2,4,5-trichlorophenoxyacetic acid, a defoliation component of Agent Orange, hinting at the origin of clofibrate as a crop spray. Gemfibrozil, 2,2-dimethyl-5-(2,5-

**Table 1**

Survival and mortality in the main fibrate trials, treatment compared to control

Trial Year reported	WHO [21] 1978	FIELD [22] 2005	HHS [23] 1987	BIP [24] 2000	VA-HIT [25] 1999	LEADER [26] 2002
<b>Fibrate used and daily dose</b>	Clofibrate 1600 mg	Fenofibrate 200 mg	Gemfibrozil 1200 mg	Bezafibrate 400 mg	Gemfibrozil 1200 mg	Bezafibrate 400 mg
<b>Deaths/active, Rx</b>	162/5331	356/4895	45/2051	161/1548	198/1267	204/783
<b>Survival, %</b>	96.96	92.73	97.81	89.60	84.37	73.95
<b>Deaths/placebo control</b>	127/5296	323/4900	42/2030	152/1542	220/1264	195/785
<b>Survival, %</b>	97.60	93.41	97.93	90.14	82.59	75.16
<b>Absolute increase in % survival on treatment</b>	–0.64	–0.68	–0.12	–0.54	+1.78	–1.21
<b>Mortality on treatment, compared to control, %</b>	+26.7	+10.3	+6.0	+5.5	–10.2	+4.9
<b>Mean treatment, years</b>	5.2	5	5	6.2	5.1	4.6

BIP = Bezafibrate Infarction Prevention; FIELD = Fenofibrate Intervention and Event Lowering in Diabetes; HHS = Helsinki Heart Study; LEADER = Lower Extremity Arterial Disease Event Reduction; VA-HIT = Veterans Affairs HDL Intervention Trial; WHO = World Health Organisation.

xylyloxy)valeric acid, is similar in structure, though not halogenated. All four have similar organic solvent/water solubilities with Log *P*'s in the range of 3.3–5.3. Nothing distinguishes these four fibrates in terms of receptor binding, primary or secondary pharmacology [35]. They all activate peroxisome proliferator-activated receptors, a group of nuclear receptors that regulate carbohydrate, lipid, protein and bone metabolism; cellular differentiation; development; and tumorigenesis. Their adverse event profile is diverse and difficult to predict, making it hard to justify a single composite safety endpoint.

The clofibrate experience set the standard for the level of evidence that would be needed for new lipid drugs. Reductions in cardiovascular morbidity and mortality need to outweigh toxicity. When reviewing the risk benefit of individual drugs, the results for the class of compound should be reviewed. None of the results in Table 1 show a significant difference between the fibrates that would distinguish individual drugs from a class effect. When medicinal chemistry and pharmacology similarities are taken into account, and the fact that the VA-HIT trial studied a more targeted population, the results suggest a fibrate class effect.

## Secondary prevention statin trials

Little positive progress in lipid pharmacotherapy was made until the statin breakthrough. In contrast to the serendipitous discovery of fibrates, with their extensive off-target pharmacology, statin compounds were tested for *in vitro* inhibition of a single target enzyme, 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCoA), to reduce cholesterol synthesis. Inhibiting intra-hepatocyte cholesterol synthesis increases the expression of LDL receptors on the hepatocyte membrane leading to increased hepatic LDL uptake, thus reducing plasma LDL [36].

The best treatment indication for any lipid therapy has been the use of statins for secondary prevention, summarized in Table 2. Meta-analyses confirms this benefit, though it can focus on lipid lowering and composite endpoints [37, 38]. Few doubt the benefit of statins for the secondary prevention of MI, though a recent meta-analysis suggested that the postponement of death by statins for secondary prevention only averaged four days [6], though individuals will vary. A suggestion that statins worsen atherosclerosis [39] is at odds with their known benefit on cardiovascular outcomes. This lack of consensus suggests a need to examine the original mortality/survival data for the main trials (see Table 2 [40–44]).

The first major lipid trial to show a convincing reduction in mortality, 4S, reported in 1994 [40]. A high risk Scandinavian population, average total cholesterol 7.5 mmol/l, showed a mean 29% reduction in mortality after about five years' treatment. This led to blockbuster sales of simvastatin and multiple large trials followed as companies competed for the statin market.

Tabulating survival data allows an across-trials comparison. Both the 4S and Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trials increased overall survival over some five to six years by just over 3% in absolute terms. This magnitude of benefit is unlikely to be repeated, as the trials were conducted in high-risk populations who were naïve to statins; now most patients with an MI will be given a statin.

Other large trials of secondary statin prevention provide useful confirmation of the 4S and LIPID results. In contrast to the other three secondary prevention trials, the survival benefit in Cholesterol and Recurrent Events study (CARE) and Aggressive Lipid-Lowering Initiation Abates New Cardiac Events (ALLIANCE) studies did not reach statistical significance. But a lack of statistical significance for mortality cannot be dismissed, as such results help interpret the likely class effect. Taking the secondary trials as a whole, in

**Table 2**

Survival and mortality in the main secondary prevention statin trials, treatment compared to control

Trial Year reported	4S [40] 1994	CARE [41] 1996	LIPID [42] 1998	HPS [43] 2002	ALLIANCE [44] 2004
<b>Statin</b>	Simvastatin	Pravastatin	Pravastatin	Simvastatin	Atorvastatin
<b>Daily dose</b>	10–40 mg	40 mg	40 mg	40 mg	40 mg
<b>Deaths/active, Rx</b>	182/2221	180/2081	498/4512	1328/10 269	121/1217
<b>Survival, %</b>	91.81	91.35	88.96	87.07	90.06
<b>Deaths/placebo control</b>	256/2223	196/2078	633/4502	1507/10 267	127/1225
<b>Survival, %</b>	88.48	90.57	85.94	85.32	89.63
<b>Absolute increase in % survival on treatment</b>	<b>+3.33</b>	<b>+0.78</b>	<b>+3.02</b>	<b>+1.75</b>	<b>+0.43</b>
<b>Mortality on treatment, compared to control, %</b>	–28.9	–8.3	–21.5	–11.9	–4.1
<b>Mean treatment, years</b>	5.4	5.0	6.1	5.0	4.5

4S = Scandinavian Simvastatin Survival Study; ALLIANCE = Aggressive Lipid-Lowering Initiation Abates New Cardiac Events; CARE = Cholesterol and Recurrent Events; HPS = Heart Protection Study; LIPID = Long-Term Intervention with Pravastatin in Ischaemic Disease.

populations with survival rates in the region of 85–90% treated for around five years, the absolute improvement in survival is roughly 2%. This is consistent with the largest secondary statin trial, the Heart Protection Study (HPS), though longer term mortality benefit was absent in this trial after 11 years mean follow-up relative risk 0.98, 95% CI 0.92–1.04 [45]. All statins target the HMG CoA enzyme and provide mutually supportive evidence for a statin class effect, irrespective of individual trial levels of statistical significance. The benefit is modest compared to the benefit of other measures, such as smoking cessation, or even the absence of exposure to passive smoking [9].

Taking a wider approach to trial interpretation [34], the statistical priors for statins are substantial. The target enzyme is relevant, the drugs have little secondary adverse pharmacology compared to fibrates. The result of the 4S study was convincing as the mortality data were fully supported by the secondary endpoints.

Table 2 shows the variability in results with the largest trial, HPS, reassuringly in the median position in terms of benefit on survival. Five out of five trials are positive in terms of mortality, supporting a class effect. There is no medicinal chemistry or pharmacodynamic reason, apart from dose potency, to suggest a difference between the statins that would influence risk benefit.

## Primary prevention statin trials

The success of the 4S trial led to trials for primary prevention, a population many times the size of the secondary prevention population. This has implications for commerce in terms of sales and also public safety in terms of increased population exposure. Primary and secondary prevention populations might be expected to show a similar incidence of adverse events with treatment. If the incidence of cardiovascular disease were ten times lower in a primary prevention population then the potential for benefit is greatly reduced, even though the risk of adverse effects is likely to be similar. Familial hypercholesterolaemia is a separate consideration, as the need for treatment is not contentious and is not considered further.

The impact of statins on primary prevention has been addressed by several meta-analyses. An analysis of 11 trials involving over 65 000 patients in high-risk primary prevention found a reduction in all-cause mortality, risk ratio, 0.91; 95% CI, 0.83–1.01 [46]. The median reduction of 9% in mortality provides good evidence of a trend, though it did not reach a conventional level of statistical significance. This study was careful to omit patients with angina, coronary disease or stroke at baseline from trials such as the West of Scotland Coronary Prevention Study (WOSCOPS) by retrospective analysis when such data were available [46].

A similar 9% reduction in all-cause mortality was shown for 27 trials analysed by the Cholesterol Clinical Trialists Collaborators (CTT) [47, 48]. This involved splitting the trial populations into five categories of baseline five-year major vascular event risk, a useful tool, but not within the trials' original protocols. Of the 27 CTT meta-analysis trials, there were five of high compared to lower dose. Both primary and secondary prevention trials were included in the remaining

22 trials. The favourable effect on all-cause mortality reported in this meta-analysis reflects a weak trend for no excess non-vascular deaths with treatment, relative risk (RR) 0.97 (95% CI, 0.88–1.07).

The Cochrane Collaboration meta-analysis on the mortality benefit of primary prevention found an odds ratio (OR) of 0.86 (95% CI, 0.79–0.94) for all-cause mortality with statins. Though this meta-analysis involved 18 trials, two trials contributed most to the result as the review gave >50% weight to the WOSCOPS trial and >22% weight to the Justification for the Use of Statins in Primary Prevention (JUPITER) trial [49]. The Cochrane conclusions may not apply to primary prevention for populations at lower risk than the West of Scotland population during an atherosclerosis pandemic (WOSCOPS). A trial stopped by interim analysis after less than two years mean treatment duration (JUPITER) may be insufficient evidence on which to base treatment that may last for potentially decades.

A more recent meta-analysis suggested that the postponement of death by statins for primary prevention, averaged across a population, was only three days [6].

It is not clear that statins used for primary prevention in low risk asymptomatic patients are of value or sufficiently safe [50]. In the substantial clinical trials, although cardiovascular events fell with statins compared to placebo, the effect on mortality was unconvincing (see Table 3 [51–57]). This is despite the participants having one or more cardiovascular risk factors and the inclusion of some patients with claudication or previous myocardial infarction. Studies varied with some seven-fold range in mortality within the placebo groups.

The lowest average survival rate in the primary prevention trials was about 88% after about five years treatment in the ALL-HAT trial [52], but the effect of treatment on survival was a statistically and clinically insignificant 0.15%. The best average survival rate was in the MEGA trial, over 98% in the placebo group [55]. The MEGA trial result was unusual in this respect and the findings in the low risk Japanese population may not transfer to other populations. The absolute increase in average survival in MEGA was a modest 0.55% [55]. An advantage of the presentation of data in Table 3 is that MEGA can be viewed as either an impressive 32% reduction in mortality, or as a change in survival from 98.34% to 98.89%. Either presentation is valid and may be used singly in meta-analysis, but when both are shown they better inform decisions on risk benefit.

Only two studies, JUPITER [54] and WOSCOPS [57], show marginally significant reductions in mortality ( $P = 0.02$  and  $0.04$ , respectively). These two studies were not strictly primary prevention. Serum cholesterol was considerably higher in WOSCOPS [57] which recruited older men in a high-risk West of Scotland population where a significant number had angina or claudication. A 20-year follow-up of WOSCOPS showed significant health benefits attributable to treatment, but a small effect on survival [58]. Patients in JUPITER [54] had elevated C-reactive protein, a possible additional risk factor. JUPITER was unusual in that the trial terminated early at 1.9 years and longer term mortality benefit was not established. A high dose of statin was employed in JUPITER, over 12-fold the dose at which LDL-cholesterol is lowered by 50% of maximum, raising the possibility of a greater



**Table 3**

Survival and mortality in the main primary prevention statin trials, treatment compared to control

Trial Year reported	AFCAPS [51] 1998	ALLHAT [52] 2002	ASCOT [53] 2003	JUPITER [54] 2008	MEGA [55] 2006	PROSPER [56] 2002	WOSCOPS [57] 1995
<b>Statin</b>	Lovastatin	Pravastatin	Atorvastatin	Rosuvastatin	Pravastatin	Pravastatin	Pravastatin
<b>Daily dose</b>	20–40 mg	40 mg	10 mg	20 mg	10–20 mg	40 mg	40 mg
<b>Deaths/active, Rx</b>	80/3304	631/5170	188/5168	198/8901	43/3866	298/2891	106/3302
<b>Survival, %</b>	97.58	87.79	96.36	97.78	98.89	89.70	96.79
<b>Deaths/placebo control</b>	77/3304	641/5185	212/5137	247/8901	66/3966	306/2913	135/3293
<b>Survival, %</b>	97.67	87.64	95.87	97.22	98.34	89.50	95.90
<b>Absolute increase in % survival on treatment</b>	<b>−0.09</b>	<b>+0.15</b>	<b>+0.49</b>	<b>+0.56</b>	<b>+0.55</b>	<b>+0.20</b>	<b>+0.89</b>
<b>Mortality on treatment, compared to control, %</b>	+3.9	−1.2	−11.9	−19.9	−32.3	−1.8	−21.7
<b>Mean treatment, years</b>	5.2	4.8	3.2	1.9	5.3	3.2	4.9

AFCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT = Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; JUPITER = Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin; MEGA = Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; WOSCOPS = West of Scotland Coronary Prevention Study.

incidence of adverse events with longer treatment. In JUPITER, 1.9 years on rosuvastatin, compared to placebo, increased survival by 0.6% ( $P = 0.02$ ). Whether the incidence of diabetes mellitus and additional declines in renal function could have reduced the benefit in a longer trial is not known; adverse events are a particular concern for prolonged treatment [59].

## Discussion

The mortality/survival data presented from three sets of cholesterol trials provide additional information about the effect of treatment on survival. Fibrate treatment in five of the six main trials was associated with a mean decrease in survival. In secondary prevention, statin treatment increased survival in all five of the main trials, absolute mean percentage increase ranged from 0.43% to 3.33%, median 1.75%. In primary prevention, statin treatment increased survival in six of the seven main trials, absolute mean percentage change in survival ranged from −0.09% to 0.89%, median 0.49%.

As treatment guidelines are evidence based and mortality data are objective, a consensus might be expected for the effect of cholesterol treatment on survival. Despite meta-analyses, aspects remain open to debate. Below are summarized both an enthusiastic view and a cautious view of how the mortality data might be interpreted. Which view is adopted determines the size of the population treated.

Enthusiasm for fibrates is supported by a meta-analysis showing a lack of detriment on all-cause mortality, OR 0%; 95% CI, −8% to 7%, with some benefit for those with higher mean baseline triglycerides [27]. Clofibrate did cause harm, but this is no longer used and is no longer relevant. No modern fibrate significantly increases all-cause mortality and it is

unrealistic for sponsors to fund trials with this as a primary endpoint. All current fibrates show statistically significant reductions in cardiovascular disease. There are adverse events, but none outweigh the benefit. The risk benefit for fibrates is positive, particularly for those with elevated triglyceride concentrations.

Enthusiasm for statins in secondary prevention starts with sound science. They target a single enzyme to inhibit cholesterol synthesis and cause a marked improvement in lipid profile [36]. Off-target pharmacology is limited. The first large trial, 4S, confirmed the predicted biochemical and cardiovascular benefits with a significant reduction in mortality in a high risk Scandinavian population with high baseline cholesterol concentrations. Since then, all major trials have shown either significant benefit, or a positive trend, in all-cause mortality. Adverse events are infrequent with no increase in non-cardiovascular mortality from meta-analysis. The statins behave as a class; there is no medicinal chemistry or pharmacodynamic reason, apart from dose potency, to suggest a difference between the statins that would influence risk benefit.

Enthusiasm for statins in primary prevention is based on the science and their success in secondary prevention. There is concordance from meta-analyses that they reduce all-cause mortality by about 9–14% in low cardiovascular risk, or primary prevention, populations [46–49]. They are safe and can be widely prescribed as there is no increase in non-cardiovascular mortality. The 2013 ACC/AHA guideline states that for primary prevention of LDL > 5 mmol/L, individuals should receive life-long statin therapy from the age of 21 as for every 1 mmol/L reduction in LDL, cardiovascular risk is reduced by 20% [5]. This represents some 40% of the UK population, where the average total cholesterol is 5.9 mmol/L [60].

Caution for the use of fibrates is rooted in their discovery by serendipity, rather than from targeting biochemistry. The

medicinal chemistry is similar across the class and reflects their crop spray origin. There are no distinguishing pharmacological differences between members of the class. A mechanism of action was discovered late in development and involves nuclear receptors, which have a range of secondary pharmacology leading to diverse adverse events. Until 1978 clofibrate was used widely; evidence from trials even cast doubt on the ethics of further placebo controlled trials [30]. There was no regulatory requirement to conduct the WHO Clofibrate study. The historical change of opinion for clofibrate, from positive to negative, influences subsequent subsequent intuitive interpretation based on this past experience, a learning technique used in programmed intelligence [61]. Failure to confirm benefit in a later, larger trial is not unusual. Another example is the use of magnesium for secondary prevention of MI. The first seven small trials showed a mortality benefit for magnesium, OR 0.44 (95% CI, 0.27–0.71) [62], yet this early enthusiasm was disproved by the results of ISIS-4 [63]. For clofibrate and magnesium, the single large trial provides better evidence than meta-analyses of earlier smaller trials. This history can be lost in meta-analyses.

As one trial powered for mortality led to the withdrawal of clofibrate, there was no commercial incentive to power later fibrate trials for mortality. The second largest trial, FIELD, showed a similar absolute percentage decrease in survival as the WHO trial, though not statistically significant. Five of the six main trials found increases in mortality. The VA-HIT trial showed a non-significant decrease in mortality, probably because of the high triglycerides and low HDL inclusion criteria, rather than a particular property of gemfibrozil.

Criticism of the use of statins for secondary prevention is limited. The secondary prevention statin trial results support a class effect, despite some trials not reaching mortality significance. Favourable trends in lower risk populations support the significant benefit in higher risk populations. An outcome model suggested that average median postponement of death in secondary prevention is a modest four days [6], making it important to know the mortality data from the original trials.

Caution for the use of statins in primary prevention starts with a criticism of the 'lower is better for cholesterol' mantra. Early attempts to draw a regression line through the placebo and active treatment points for cholesterol trials claiming a unit fall in cholesterol causes a unit fall in cardiovascular events was refined by Dr Ballantyne [64]. This was repeated in publications such as the Treat to New Targets study [65, 66], that used the regression line to support higher doses of statin, despite more deaths with the higher dose (HR 1.01; 95% CI, 0.85–1.19), possibly related to a six-fold increase in hepatic biochemical abnormalities [65].

The Ballantyne plot confuses epidemiology with intervention [65]. This makes the benefit of statins for primary prevention a contentious area [67, 68]. If a regression line is drawn only through the mean placebo data for the trials, then this line is steeper [67], yet placebo is not a better treatment than active. To understand the effect of intervention, each placebo point has to be joined with its respective trial active treatment point [39], confirming cholesterol lowering has a lesser impact on clinical events than predicted by the Ballantyne line, particularly for trials with lower baseline cholesterol.

Meta-analyses of statins in primary prevention have some limitations. The CTT meta-analysis [47] was not confined to primary prevention as it included high dose compared to a lower dose and secondary prevention trials. The retrospective split of the populations into five categories of vascular risk was not defined within the original protocols. The CTT analysis found no significant safety signal. The Cochrane meta-analysis of the mortality benefit of primary prevention was heavily weighted by just two trials and concluded that there was no evidence of any serious harm caused by statins [48]. The West of Scotland population was studied during an atherosclerosis epidemic [57] and the JUPITER trial was criticized for early termination following interim analysis [69].

Any meta-analysis combines different trial populations. The two bezafibrate trial results (Table 1), could be combined, but separately they show the same trend in different populations. The two gemfibrozil results (Table 1), could be combined for the mortality effect to be neutral, but this would lose an explanation that the high triglyceride/low HDL population is a better target for fibrates. Including the VA-HIT result in a meta-analysis might not be justified, given the differences in baseline lipid profiles. The data in the tables also show how different the trial populations were, such as 75% survival on placebo in LEADER compared to 98% survival in HHS (Table 1), details that can be lost in meta-analysis.

The lack of detriment on non-cardiovascular mortality in meta-analyses of statin primary prevention is reassuring. In clinical practice biochemical monitoring is less intense, reducing early withdrawals. Adverse events with long-term statin treatment include an increase in diabetes in a healthy cohort (OR 1.87; 95% CI, 1.67–2.01) [70]; an increase in diabetes with complications (OR 2.50; 95% CI, 1.88–3.32) [70]; and an increase in diabetes in men with metabolic syndrome (OR 1.46; 95% CI, 1.22–1.74) [71]. A pooling of five trials showed an increase in adverse hepatic events with intensive statin treatment compared to moderate statin treatment (OR 3.73; 95% CI, 2.11–6.58) [72]. In a long-term cohort statins were associated with acute kidney injury (OR 1.30; 95% CI, 1.14 to 1.48); chronic kidney disease (OR 1.36; 95% CI, 1.22 to 1.52); and nephritis/nephrosis/renal sclerosis (OR 1.35; 95% CI, 1.05 to 1.73) [73]. What is absent from these numbers is a composite endpoint of these safety events to balance the use of composite endpoints when measuring efficacy. This opens a debate as to the long-term safety of statins and how best to weigh the efficacy/safety balance.

What weighting is given in meta-analyses to the numbers recruited, the number of events or the duration of treatment is not fixed. Retrospective significance testing is limited, as statistics should follow a hierarchy of endpoints pre-defined in the original protocol taking into account multiplicity. Mortality is nonetheless a key endpoint when a disease may be fatal as a summary of risk benefit, being a useful illustration of class effects. The reported mortality/survival data for the major trials do not replace meta-analyses, but provide an additional view of the data. The Number Needed to Treat, or the Number Needed to Harm, are also useful measures, though they may reflect a large effect for a few individuals, rather than a small effect for the majority. For this reason the calculation of the postponement of death has been calculated, a median effect of 3 days for statin primary prevention

and 4 days for statin secondary prevention, though this has the disadvantage of being the average [6].

The database for the main lipid trials supports the lipid hypothesis; pharmacological improvements in lipid profiles can reduce cardiovascular events. Given the reliance by guidelines on biomarkers and the imbalanced use of composite endpoints, the mortality/survival data for the main trials deserve attention as cardiovascular disease is common and often fatal. Consumers should know a rough estimate of whether therapy affects life expectancy.

In contrast to lipid therapy, the reductions in coronary events and stroke with antihypertensive pharmacotherapy closely approximate those predicted by the blood pressure levels in published epidemiology [74]. Antihypertensive pharmacotherapy consistently reduces total mortality [74]. In 147 long-term clinical trials, all major antihypertensive drug classes conferred similar benefits [75].

Survival data provide a useful summary of class effects. Interpretation is enhanced by knowledge of the history of the database and of chemistry and pharmacology. The data for fibrates do not disprove that a detrimental effect on mortality is a class effect. Primary prevention with statins has not been shown to prolong long-term survival for the large section of the otherwise healthy population for whom many now recommend it. Familial hypercholesterolaemia is a separate issue and outside the remit of this paper. For secondary prevention with statins in high risk populations, the benefit on survival is significant, though not increased by higher doses [76] and small compared to the loss of more than a decade of life for the average smoker.

## Competing Interests

All authors have completed the Unified Competing Interest form at [http://www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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